FIG. 1

$$R_1$$
 R_2

			Cruzain	<i>T.cruzi</i> Survival	Host
Cmpd#	R1	R2	IC50 (μM)		Toxicity
1a	2'-phenyl	NH ₂	>20	5 days	none
1b	3'-phenyl	NH ₂	8	43 days	none
1c	4'-phenyl	NH ₂	5	8 days	toxic
2a	2'-NH-phenyl	NH ₂	>20	5 days	none
2b	3'-NH-phenyl	NH ₂	>20	43 days	none
2c	4'-NH-phenyl	NH ₂	>20	43 days	none
2d	3'-O-phenyl	NH ₂	10	27 days	toxic
2e	4'-O-phenyl	NH ₂	10	28 days	toxic
3d	3'-Br	NH ₂	0.06	43 days	none
3e	3'NH ₂	NH_2	>20	5 days	none
3f	2'-OH	NH_2	>20	5 days	none
3g	3'-OH	NH_2	>20	5 days	none
3h	4'-OH	SMe	>20	5 days	none
4a	3'-Br	Shit	>20	7 days	toxic
4c	3'-Br	piperidyl	5	5 days	none
4d	3'-Br	N-methylpiperazinyl	5	14 days	toxic
4e	3'-Br	NEt ₂	5	5 days	none

FIG. 2

$$R_1$$
 R_2
 R_3
 R_4

							•	T.cruzi	
							Cruzain	Survival	
Cmpd#	R	RI	R2	X	Y	Z	IC50(μM)	(days @5μM)	Host Toxicity
3a	Н	H	NH ₂	N	CH	CH	>20	43 days	none
3b	H	H	NH ₂	CH	N	CH	>20	5 days	none
3c	H	H	NH ₂	CH	CH	N	>20	5 days	none
4b	H	H	SMe	N	CH	CH	>20	5 days	none
3i	CH(Me)NNHC(S)NH ₂	H	NH_2	CH	CH	CH	5	5 days	none
3j	CH(Me)NNHC(S)NH ₂	H	NH _s	N	CH	CH	>20	5 days	none
3k	CH(Me)NNHC(S)NH ₂	Me	NH ₂	CH	CMe	N	>20	5 days	none

FIG. 3

Cmpd#	Rl	R2	Rhodesain IC50(µM)	<i>T.brucei</i> ED50 (μΜ)
la	2'-phenyl	NH ₂	>20	>20
1b	3'-phenyl	NH_2	1.1	12
lc	4'-phenyl	NH_2	0.09	10
2a	2'-NH-phenyl	NH_2	>20	>20
2 b	3'-NH-phenyl	NH_2	0.8	8
2c	4'-NH-phenyl	NH_2	18	4.5
2 d	3'-O-phenyl	NH_2	0.55	6
2e	4'-O-phenyl	NH_2	8	3
3d	3'-Вг	NH_2	0.05	>20
3e	$3'NH_2$	NH_2	>20	>20
3f	2'-OH	NH_2	>20	>20
3g	3'-OH	NH_2	>20	>20
3h	4'-OH	NH_2	>20	>20
4a	3'-Br	SMe	>20	10
4c	3'-Br	piperidyl	4	3
4d	3'-Br	N-methylpiperazinyl	4	2
4e	3'-Br	NEt ₂	1.8	3

FIG. 4

C 4#	D	R1	R2	v	v	Z	Rhodesain	T.brucei
Cmpd#	R	K1	KZ	<u> </u>	<u></u>		IC50(uM)	ED50 (uM)
3a	Н	H	NH ₂	N	CH	CH	>20	4
3b	${f H}$	H	NH_2	CH	N	CH	>20	>20
3c	\mathbf{H}	H	NH ₂	CH	CH	N	>20	>20
	H	H	SMe		CH	CH	>20	0.3
3 i	CH(Me)NNHC(S)	H	NH2			CH	0.33	>20
4b 3i 3 <u>j</u>	CH(Me)NNHC(S)	H	NH ₂	N	CH	CH	>20	>20
3k	CH(Me)NNHC(S) NH ₂	Me	NH ₂	CH	CM	eΝ	>20	>20

FIG. 5

$$R_1$$
 R_2

Cmpd#	R1	R2	Falcipain 2 IC50(μM)	P.falciparum ED50(μM)
1a	2'-phenyl	NH ₂	>20	>20
1Ъ	3'-phenyl	NH ₂	>20	>20
1c	4'-phenyt	NH ₂	10	>20
2a	2'-NH-phenyl	NF ₂	>20	>20
2 b	3'-NH-phenyl	NH_2	>20	>20
2c	4'-NH-phenyl	NH ₂	>20	9.9
2 d	3'-O-phenyl	Nm_2	>20	>20
2e	4'-O-phenyl	NH ₂	>20	>20
3d	3'-Br	NH ₂	>20	>20
3e	3NM ₂	NH ₂	>20	>20
<u>.</u> 3f	2'-OH	NH ₂	>20	>20
3g	3'-OH	NH ₂	>20	>20
3h	4'-OH	NH ₂	>20	>20
4a	3'-Br	SMe	>20	>20
4c	3'-Br	piperidyl	>20	20
4d	3'-Br	N-methylpiperazinyl	>20	4
4e	3'-Br	NEt ₂	>20	>20

FIG. 6

FIG. 7

Compound	Structure	Surviv 5 mgs/kg weight	al (toxicity) 20mgs/kg weight
3a	N H NH2	20 hours (*)	62 hours (**)
4b	N H s	62 hours (No)	62 hours (No)
3j	NH ₂	62 hours (No)	62 hours (No)
	SNH		
2c	NH ₂ NH ₂ NH ₂	62 hours (No)	62 hours (No)
4d		62 hours (No)	62 hours (No)
1b	Br NH ₂	62 hours (No)	62 hours (No)

^{*}Animal suffered toxic shock after injection, characterization by tremor, loss of mobility, malaise, and death

^{**}Animal survived treatment with malaise, loss of mobility and ruffled hair after injection

FIG. 8

			<u> </u>
Structure	Cruzain IC50 (µM)	Rhodesain IC50 (µM)	P. falciparum W2 IC50 (µM)
N N NH2	1.5	0.4	>20
H SCH ₃	>10	>10	>20
O N N NH2	>10	9	>20
N NH2	0.312	5	>20
N N N N N N N N N N N N N N N N N N N	>10	not determined (ND)	>20
H SOH	>10	>10	>20
N H N N N N N N N N N N N N N N N N N N	>10	>10	>20
H H I N N N N N N N N N N N N N N N N N	>10	· >10	3.3
S NN NH ₂	>10	5	>20
S NNNNNN H H	>10	>10	7.7

Structure	Cruzain IC50 (µM)	Rhodesain IC50. (µM)	P. falciparum W2 IC50 (µM)
NN NHZ	>10	>10	>20
N N N N N N N N N N N N N N N N N N N	>10	>10	>20
O N N NHE	>10	>10	>20
N N N N N N N N N N N N N N N N N N N	5	0.8	2.5
HIN N N	>10	ND	>20
O H CI	>10	>10	0.489
NH CI	>10	>10	0.125
NH CI	>10	>10	0.227
	>10	>10	0.961

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (µM)	P. falciparum W2 IC50 (μM)
TOPO	>10	>10	0.908
	>10	>10	0.794
S NH ₂ NH NH-NH-NH-NH	2	4	0.051
N N N N N N N N N N N N N N N N N N N	ND	ND	0.242
	>10	8	0.957
F C NH	ND	4	1.193
	ND	3	1.809
	ND	1	1.226

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (µM)	P. falciparum W2 IC50 (µM)
F.CO. C. H. H. HALL	ND	5	0.833
N-WH N-WH	ND	ND	>20
S NT	ND	ND	>20
N-NH ₂ N-NH ₂	ND	ND	>20
N-NH N-NH N-NH	ND	ND	>20
N-NH ₂ N-NH ₂	ND	ND	>20
N-NH N-NH O N	ND	ND	>20
Quil s	ND	4	0.025

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (μΜ)	P. falciparum W2 IC50 (μM)
Christon Christon	1.8	0.11	0.008
CAPAN NO	1.6	4	0.028
N N N N N N N N N N N N N N N N N N N	ND	ND	0.013
Churt Ch	ND	0.7	0.013
	ND	ND	0.212
Ly hy h	ND	1.8	0.26
CANNAN HONO	ND	0.42	0.212
	ND	ND	0.19
H ₂ N N N N N N N N N N N N N N N N N N N	ND	4	6.521
HEN H NHY H NHY	ND	5.5	0.14

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (µM)	P. falciparum W2 IC50 (µM)
	>10	ND	0.032
S N N N N S H	1.5	0.3	1.677
H S H S H C	0.8	0.4	0.054
Fe N-NH S H ₂ N	8.5	ND	>20
Fe N-NH H ₂ N	ND	ND	>20
HN-N Fe S=NH ₂ N-NH H ₂ N	3.5	4.2	>20
HN-N Fe N-NH H ₂ N	ND	ND	>20
HN-N Fe S=NH ₂ N-NH H ₂ N	2	1.8	>20

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (µM)	P. falciparum W2 IC50 (µM)
HN-N Fe N-NH H ₂ N	ND	ND	>20
Fe N-NH S H ₂ N	>10	10	>20
Fe N-NH H ₂ N	ND	ND	>20
Fe N H N N	ND	ND	0.0246
Fe HN N-N N=	ND	ND .	0.0161
HO N N NH ₂	9	4	>20
HO N N NH2	2.1	2	>20
HO N-N-N-N-NH ₂ OH H	5	3	>20

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (μΜ)	P. falciparum W2 IC50 (μΜ)
ON N N NH2	20	10	>20
HO N-N-N-NH ₂	ND	7	>20
CI HO N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-	ND	1	0.376
CI HO N-N-N-NH ₂ OH H	ND	>10	0.246
HO N.N NH ₂ OH H	ND	ND	>20
HO N'N S	ND	ND	>20
THO OH H H ON NH	ND	5	0.437
OH H H HO N'N N N N NH N'N NH	2.8	2.5	1.065

Structure	Cruzain IC50 (µM)	Rhodesain IC50 (µM)	P. falciparum W2 IC50 (µM)
HO OH H H	1.8	1.8	0.265
HO OH H H	>10	>10	0.113
HO OH H H	ND	ND	0.376
CI HO OH H H	3.5	ND	0.077

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- خدسته بریج						
Therapeutic	Index	1	200	7	9643	526
Cytotoxicity	ED ₅₀ µg/ml	0.04	0.3	1.8	13.5	10
	repeat	0.0384 ± 0.0004	0.0015± 0.0005	0.265 ± 0.66	0.0014 ± 0.0005	0.019 ± 0.009
EDso µg/ml	+/- 95% CL	<1.11 ®	<1.11 ®	-1.11 ®	<1.11 ®	<1.11 ®
	1	29.66	99.73	98.51	98.45	99,39
bition ucei	3	99.57	99.68	100	99.95	99.52
% inhibition T. brucei	10	98.85	99.22	100		99.54
	30	98.24	98.76	97.78	100	99.72
Compound	Qj	MC 156	MC 158	MC 159	MC 162	MC 164
Compound Structure		5 4' 3' 1 S' 1 S' 1 S' 1 N 2 N N N N N N N N N N N N N N N N N	SHNNNNN	SHAN	S N N N N N N N N N N N N N N N N N N N	N S H N N N N N N N N N N N N N N N N N

Therapeutic	xepul		•	0	27	20222	159
Cytotoxicity	ED ₅₀ µg/ml	>300	×300	0.57	3.08	18.2	2.9
	repeat		0.552 ± 0.156	1.331 ± 0.045	0.0537 ± 0.004	0.0009 ± 0.0005	0.0182 ± 0.0012
EDso µg/ml	+/- 95% CL	>30	<1.11®	<1.11 @	<1.11®	<1.11 ®	<1.11®
	-	7.3	94.85	82.42	99.78	98.74	98.73
bition ucei	က	10.09	99.23	98.27	99.92	98.46	99.74
% inhibition T. brucei	10	12.89	60'66	99.25	99.87	98.31	99.76
	30	15.25	99.84	99.23	100	97.82	99.44
Compound	QI	MC 172	MC 172B	MC 176	MC 177	MC 184	MC 186
Compound Structure		H ₂ N H N N H ₂ N	H ₂ N H N H N ₂ N H N N N ₂ N H N N N N N N N N N N N N N N N N N N	N H N N N N N N N N N N N N N N N N N N	S N N N N N N N N N N N N N N N N N N N		Mes N'N N SMe